

Celiac Disease Overlooked in a Patient With Becker Muscle Dystrophy

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Abstract

Becker Muscle dystrophy is a regressive orphan X-linked disease that will progress into hypotonia and muscle weakness involving the skeletal as well as the cardiac muscles, with increased CPK blood levels and hypertransaminasemia. Patients with Becker muscle dystrophy rarely present symptoms at early age. Here we present a patient with Becker dystrophy, increased ALT and marked digestive symptoms. The digestive symptoms were proven to be linked to a celiac disease that was overlooked due to the presence of the muscle dystrophy. It is not uncommon in areas with very high consanguinity rates to have a patient presenting two rare genetic diseases at the same time. The initiation of a gluten free diet helped improve the symptoms and the wellbeing of this patient.

Keywords

Celiac disease; Becker muscular dystrophy; Lebanon.

Abbreviations

- CD: Celiac Disease
- BMD: Becker muscular Dystrophy
- ALT: Alanine aminotransferase
- AST: Aspartate transaminase
- CPK: Creatine phosphokinase

Introduction

Becker Muscular Dystrophy (BMD), like Duchenne muscular dystrophy, are X-linked diseases due to mutation of the DMD gene, which consists of 79 exons encoding the dystrophin protein. Duchenne dystrophy, the more severe and more common form, with more severely depressed expression of dystrophin, is reported to have an incidence ranging from 1:3802 to 1:6291.2. BMD is about one-third in frequency of occurrence worldwide [1]. The frequency in the Arab world is not clearly established and currently no official data is available for the Lebanese population, estimations remain related to personal information [2,3].

Dystrophin acts as an anchor between the cytoskeleton and the extracellular matrix preserving the cellular membrane integrity, in association with the dystroglycans and the sarcoglycans. Absence or decrease of dystrophin initiates a cycle of cellular apoptosis leading to destruction of rhabdomyocyte cells, fibrosis and fatty replacement of the muscles [1]. BMD being the mild allelic form resulting from an in-frame exon deletions of the DMD gene leads to a mutant dystrophin, partially functional, resulting in a milder clinical form than Duchenne dystrophy [4]. The main clinical symptoms would be motor ranging from mild muscle weakness in BMD to more severe weakness and complete gait loss with early death due to cardio respiratory failure in the Duchenne forms. The diagnosis is prompted by the clinical presentation as well as by the finding of elevated Creatine Phosphokinase (CPK) levels and mild elevation of transaminase enzyme levels, Alanine Aminotransferase (ALT) and Aspartate Transaminase (AST).

Even though the most commonly reported symptoms in muscle dystrophy are motor, cardiac and respiratory; yet, digestive symptoms like delayed gastric emptying and intestinal pseudo-obstruction have been also reported and have been linked to the functional impairment of smooth muscle in the gastrointestinal tract [5].

However, when increased transaminase as well as digestive symptoms is noted, celiac disease remains the first differential diagnosis to be considered. Celiac disease (CD) is associated with exposure to gluten protein resulting in intestinal mucosal lesions in persons with predisposition mostly genetic or autoimmune [6]. CD can present with a constellation of variable signs and symptoms either digestive like bowel dysmotility or extra intestinal

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like fatigue, pain, anemia, osteopenia and failure to thrive [7]. Celiac disease can also be associated with hypertransaminasemia, an imbalance that is not exclusive to hepatic disorders but also noted in muscle diseases as well as with thyroid dysfunction [8].

Case report

Here we report clinical and histological findings in a 5 year old boy, who was referred to our department for follow up of persisting episodes of fatigue, bilateral quadriceps pain during the night, poor weight gain, constipation and occasional episodes of abdominal pain, but mainly for his motor complaints.

The child is a term boy, born by normal vaginal delivery, the product of an uneventful pregnancy to two none consanguineous parents of Palestinian and Algerian origin. In the family history, the maternal grandfather was diagnosed with a myopathy at the age of 40 years that was not investigated appropriately except by an EMG that showed a myopathic process.

The child had a normal neurodevelopment, and was following correctly his milestones, until the age of 3 years when he started to show mild fatigability when climbing the stairs. At 4 years of age the patient started to need to take breaks during his play time in order to relax. The patient is reported to have persisting episodes of constipation not relieved by regular diet changes, and he is able to tolerate prolonged episodes of fasting. The family history of myopathy led the parents to attempt to rule out this specific diagnosis at first.

On physical exam the child is shown to follow the 5th percentile on his growth curve since the age of 9 months, with a mild drop from the 10th percentile curve that he was following since birth. The child had a mild hypotonia of the lower limbs, and showed a mild Gowers sign upon standing. He had brisk reflexes and a clear bilateral pseudohypertrophy of his calves, a mild lordosis was noted as well. The rest of the physical exam showed no anomalies except for a non-painful mild abdominal distension.

A first blood work up was performed and showed a lactate level of 3.4 mmol/L, pyruvate of 0.011 mmol/L, AST 128 IU/L, ALT 221 IU/L, and a CPK level of 6215 IU/L. The chromatography of amino acids in blood and organic acids in urine showed no anomalies. The results were verified in a fasting state and away from strenuous activity and showed a normalization of the lactate level of 1.2 mmol/L and a persisting increase of transaminase level as well as the CPK level, with AST 118 IU/L, ALT 217 IU/L, and a CPK level of 2115 IU/L.

A muscle biopsy was then done. Immunohistochemical studies using antibodies to different muscle sarcolemmal proteins illustrated impaired, reduced and uneven expression of dystrophin [Figure 1 -2] with an antibody to the amino-terminal (N) of the Dystrophin gene [Figure 3], while anormal expression of Dystrophin was demonstrated with antibodies to the rod domain and to the carboxy-terminal domain (C-terminus) of the gene [Figure 4], changes consistent with the less severe Becker's type of dystrophinopathy.

With the diagnosis of Becker disease, most of the patient's clinical

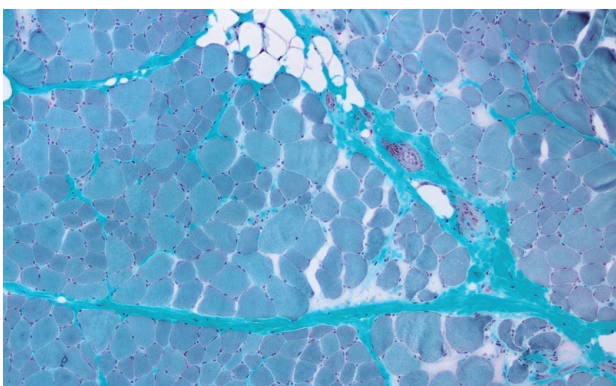


Figure 1: Gomori stain of the patient's muscle biopsy showing dystrophic changes.

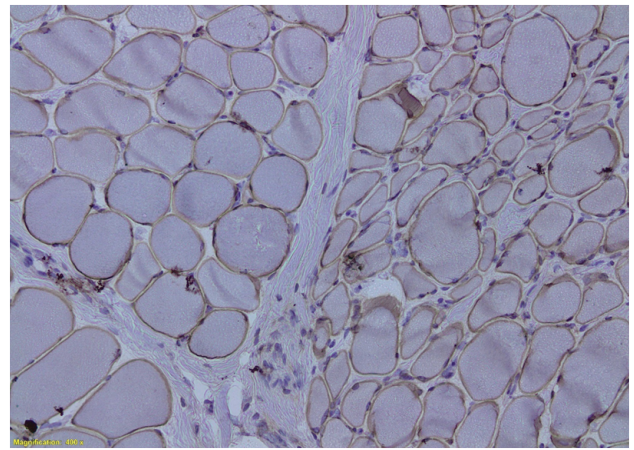


Figure 2: Immunohistochemical studies using antibodies to different muscle sarcolemmal proteins with impaired, reduced and uneven expression of dystrophin.

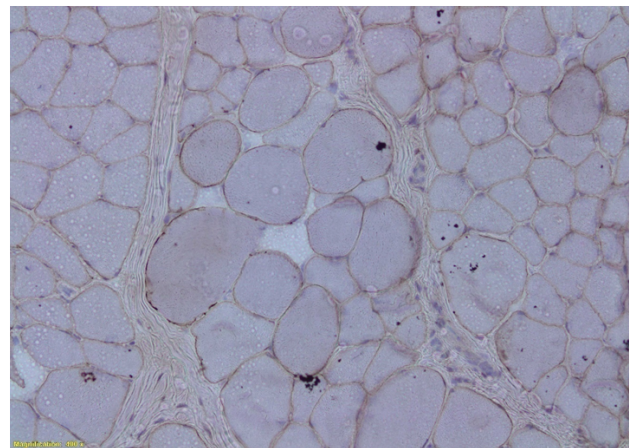


Figure 3: Immunohistochemical studies using antibodies on muscle biopsy showing reduced and uneven expression of dystrophin with an antibody to the amino-terminal (N) of the Dystrophin gene.

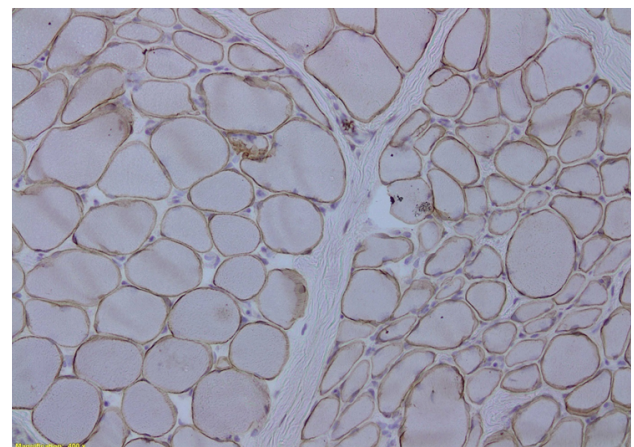


Figure 4: Immunohistochemical studies using antibodies on muscle biopsy with a normal expression of Dystrophin was demonstrated with antibodies to the rod domain and to the carboxy-terminal domain (C-terminus) of the gene.

signs were attributed to this entity and physical therapy follow up was started as well as a cardiac follow up and a nutritional follow up for the catch up with his growth.

An adequate diet was followed accurately; yet, the patient kept having the digestive symptoms described earlier, without any correction of his growth curve. After 6 months with the new diet the patient's weight dropped below the 5th percentile on the growth curve, and the child kept having a level of ALT twice the level of AST. An associated diagnosis was supposed to be considered. We completed the patient's work up for celiac disease and the blood work up showed a high level of IgG anti-gliadin 97 RU/ml and a normal IgA anti-gliadin level. The patient had also a very high IgG anti-transglutaminase level at 43.2 RU/ml and a normal IgA anti-transglutaminase level. We had to proceed with the gastrointestinal system investigations. The duodenal muscle biopsy showed flattened mucosa over Brunner's glands featuring increase density of intra epithelial lymphocytes > 40%. The esophageal biopsy showed papillomatous vascular papillary congestion and discrete inflammatory cell exocytosis. The biopsy findings were consistent with celiac disease.

After the duodenal biopsy the patient was put on a strict gluten free diet, and in a span of 2 months the child had no more distension or constipation, and started to show a growth catch up on his curve. One year of diet brought up the child's weight, which is now stable on the 25th percentile in weight. We noted as well the disappearance of the muscle cramps during the night after the initiation of the diet, as well as with the starting of the adequate physical therapy, but we note also a clear decrease in the episodes of fatigue the patient had been experiencing, even though hypotonia is still present as well as the Gowers sign upon physical exam. Repeated measures of the liver enzymes showed a stabilization of both ALT and AST between 75 and 120 IU/L.

Discussion

Like most of the Middle Eastern countries, Lebanon presents a population with a very high consanguinity reaching 70% in some areas [1]. This high consanguinity rate in our society raises the possibility of multiple concomitant rare diseases in a single person as well as in a single family leading to many cases being frequently reported [9]. In this patient the diagnosis of BMD could not explain the digestive symptoms that this patient was experiencing, which led us to seek another rare disease in the same patient.

We have very few information about the digestive system symptomatology in dystrophinopathies, even though this entity was widely studied in the early 90s of the past century, but never backed up with large scale studies.

Most of the studies were reported in the severe forms of Duchenne Myopathy rather than in BMD. Some pathological studies had already shown "significant gastrointestinal smooth muscle degeneration in Duchenne muscular dystrophy", with the presence of smooth muscle degeneration with replacement by adipose and connective tissue in the muscular layers of the stomach and the intestines, as found on post mortem biopsies in muscular dystrophy patients.

And while small scale studies had shown presence of gastric hypomotility in Duchenne Myopathy patients, Korman et al found no impairment in the small intestinal transit time, and attributed the digestive symptoms to the immobility of the muscle dystrophy patients as well as their abdominal musculature weakness [5,10].

However, in a more recent study, the oro-cecal transit time in patients with Duchenne dystrophy was proven to be actually delayed [11], and this increase in the gastrointestinal transit time has been attributed to the alterations of the myenteric plexus associated with reduced myoelectrical slow wave activity [12], as well as the reduced availability of nitric oxide due to lack of dystrophin, leading to the suppression of the Calcium dependent membrane channels in charge of the continuous activity of the intestinal smooth muscles [13].

However, most of the studies were performed on Duchenne myopathy patients, who logically present a much more severe condition than our BMD patient.

Regarding the remaining of our exams, lactic acidosis can be due to a secondary mitochondrial dysfunction noted in Duchenne myopathies, as well as the less severe Becker disease. But the hypertransaminasemia which was expected like in any myopathy patient, still showed an ALT level persistently higher than the AST level. This unusual feature led us to consider other diagnostic entities [14].

Celiac disease remains an important and common cause of cryptogenic hypertransaminasemia in 4-6% of the cases; earlier studies even report 9% of the patients with CD having hypertransaminasemia [15-17].

Patients who present malabsorption and severe duodenal lesions are more at risk of hypertransaminasemia, which responds to a gluten free diet, leading to a drop in the values of transaminases and a way to avoid progression to a manifest liver disease [18,19].

Hypertransaminasemia in CD is mainly attributed to the disruption of the integrity and function of the intestinal epithelium, leading to liver toxicity [20]. The liver enzymes disturbances as well as the clinical signs are also associated with the amount of intake of gluten, and in the Middle Eastern cuisine wheat and barley constitute major components of the daily meals which leads to more severe symptoms in Middle Eastern CD patients than in European patients [7].

In the case of our patient, the BMD was not responsible for most daily complaints aside from the hypotonia. Regular, none intensive, physical therapy sessions helped improve or yet stabilize the muscle strength, but a significant effect on the weight, the abdominal distension, the constipation and especially the fatigue was noted only after the introduction of the gluten free diet. Improvement of the ALT level was expected with the introduction of the diet, even though he failed to return to a regular baseline due to the underlying muscle dystrophy.

Conclusions

Muscle dystrophies, most specially the dystrophinopathies, are very common entities in the Middle East and the Arab world, being a very debilitating disease, as most of the clinical symptoms in the patient end up being attributed to the myopathy. But in an area with very high consanguinity rates, the probability of having two different rare disorders in the same patient should always be considered and every symptom should be thoroughly investigated.

In the case of our patient with Becker dystrophinopathy the treatment of the associated celiac disease helped to alleviate the symptoms of the patient by improving his well being.

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